PTO/SB/33 (07-05)
Approved for use through xx/xx/200x. OMB 0651-00xx
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number: 08191-0018001
	Application Number 09/872,836	Filed June 1, 2001
	First Named Inventor Shikha Barman et al.	
	Art Unit 1633	Examiner Fereydoun Ghotb Sajjadi

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record 47,443
(Reg. No.)

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34

/Jack Brennan/
Signature

Jack Brennan
Typed or printed name

(212) 765-5070
Telephone number

August 17, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ Total of no. forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Shikha Barman et al.	Art Unit	: 1633
Serial No.	: 09/872,836	Examiner	: Fereydoun Ghotb Sajjadi
Filed	: June 1, 2001	Conf. No.	: 3677
Title	: DELIVERY SYSTEMS FOR BIOACTIVE AGENTS		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants submit this request under the Pre-Appeal Conference Pilot Program described in the U.S. Patent and Trademark OG Notice, "New Pre-Appeal Brief Conference Pilot Program," dated July 12, 2005, and extended until further notice as of January 10, 2006. This request is being filed with a Notice of Appeal.

Status of Claims and Summary of Rejections

Claims 1-16, 21-29, 31-34, and 37 are pending in the application. Claims 5 and 25 have been withdrawn from consideration. In the final Office Action dated April 16, 2009, claims 1-4, 6-16, 21-24, 26-29, 31-34, and 37 were rejected as obvious.

Rejections Under 35 U.S.C. §103(a)

At pages 2-8 of the final Office Action, claims 1-4, 6-16, 29, 32-34, and 37 were rejected as unpatentable over Papahadjopoulos et al, U.S. Patent No. 6,803,053 ("Papahadjopoulos") taken with Rolland et al., U.S. Patent No. 6,040,295 ("Rolland") and further in view of Lunsford et al., U.S. Published Application No. 2002/0182258 ("Lunsford"). In addition, claims 1-4, 6, 7, 9-16, 26, 29, 32-34, and 37 were rejected as unpatentable over Papahadjopoulos taken with Rolland and further in view of Mathiowitz et al., U.S. Patent No. 6,677,313 ("Mathiowitz").

The Office Action stated that "it would have been *prima facie* obvious for one of ordinary skill in the art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date: August 17, 2009

Papahadjopoulos *et al.*" The Office Action used substantially similar language in the obviousness rejection citing the combination of Papahadjopoulos, Rolland, and Mathiowitz.

Independent claims 1 and 21 are each directed to a microparticle that is less than about 100 microns in diameter and contains at least the following: (i) a polymeric matrix; (ii) a lipid having a pKa of less than about 2.5; and (iii) a nucleic acid molecule.

Papahadjopoulos describes cationic lipid:nucleic acid complexes containing, among other components: (a) a cationic lipid; (b) a nucleic acid; and (c) a hydrophilic polymer. The Office Action dated January 25, 2005, asserted that Papahadjopoulos anticipated claim 1 and selected dependent claims. Applicants successfully overcame that rejection based at least in part on the following distinction between the claimed microparticles and Papahadjopoulos:

> First, the claimed microparticles contain a polymeric "matrix" (e.g., a material in which something is enclosed or embedded). There is no indication in Papahadjopoulos that the hydrophilic polymer used therein forms a "matrix." Rather, as noted in the passage from Papahadjopoulos cited by the Examiner on page 3 of the Office Action, "the hydrophilic polymer locates and is incorporated into hydrophobic pockets" in the cationic lipid:DNA complex.

In withdrawing the anticipation rejection, the Examiner apparently acknowledged the correctness of applicants' position, stating that "[i]n view of Applicants' arguments and upon further consideration of the claim limitation 'a polymeric matrix', the rejection is hereby withdrawn." See page 2 of Office Action dated February 22, 2007. However, the present Office Action appears to again ignore the distinction between a "polymer" and a "polymeric matrix." For example, page 3 of the present Office Action refers to "PEG-DSPE, which is a polymeric matrix." In addition, page 3 of the present Office Action incorrectly asserts that column 10, lines 26-30 of Papahadjopoulos describes a "polymeric matrix." PEG-DSPE is a polymer, not a polymeric matrix. Nothing in Papahadjopoulos indicates that PEG-DSPE is used in such a way that it forms a "polymeric matrix."

According to Papahadjopoulos, the reason that a hydrophilic polymer (such as PEG-DSPE) is incorporated into its cationic lipid:nucleic acid complexes is for the purpose of preventing the complexes from aggregating during storage and, as a result, increasing the shelf life of the complexes. The hydrophilic polymer's function in preventing aggregation of the cationic lipid:nucleic acid complexes is emphasized throughout Papahadjopoulos as an important

advantage of the invention (see Papahadjopoulos at, e.g., column 13, lines 26-49, column 18, lines 32-40, and column 29, lines 30-36). This function of the hydrophilic polymer in the cationic lipid:nucleic acid complexes of Papahadjopoulos must be considered in evaluating whether the person of ordinary skill in the art would have had any reason to include the hydrophilic polymer component in the combination proposed in the Office Action. Such a reason must exist and must be articulated by the Examiner in order for there to be *prima facie* obviousness.

As applicants' have emphasized in several prior responses, the person of ordinary skill in the art would have had no reason to make the modifications proposed by the Examiner, i.e., to entrap a PEG-DSPE-containing complex disclosed in Papahadjopoulos within a microparticle described in Lunsford or Mathiowitz.

Lunsford describes microparticles containing a polymeric matrix, a nucleic acid, and a lipid. Similarly, Mathiowitz describes microparticles containing a polymeric matrix and a nucleic acid. As noted above, the reason for including a hydrophilic polymer (e.g., PEG-DSPE) in the cationic lipid:nucleic acid complexes of Papahadjopoulos was to prevent aggregation of the complexes. The need to prevent cationic lipid:nucleic acid complex aggregation would clearly be absent if a cationic lipid:nucleic acid complex of Papahadjopoulos were to be entrapped in a microparticle of Lunsford or Mathiowitz (i.e., the cationic lipid:nucleic acid complexes would be entrapped within microparticles and thus would be unable to aggregate). Because of the particularized anti-aggregation function mediated by Papahadjopoulos's hydrophilic polymer, and the irrelevance of that function in the microparticles of Lunsford and Mathiowitz, the skilled person would have had no reason to entrap a hydrophilic polymer-containing cationic lipid:nucleic acid complex of Papahadjopoulos in a microparticle of Lunsford or Mathiowitz. Even if one were to attempt to entrap a simple cationic lipid:nucleic acid complex of Papahadjopoulos in a microparticle of Lunsford or Mathiowitz, the skilled person would have had no reason to also include a hydrophilic polymer (such as PEG-DSPE) in that entrapped composition. The need to prevent aggregation of cationic lipid:nucleic acid complexes that was the rationale for Papahadjopoulos's inclusion of a hydrophilic polymer in its complexes would be absent in Lunsford's and Mathiowitz's microparticle formulations. As a

result, the skilled person would have had no reason to create the combined composition suggested in the Office Action.

The present Office Action's only apparent reference to applicants' argument above (which has been presented in several prior responses) is the statement that "[t]he reason for inclusion of a hydrophilic polymer and PEG-DSPE in the microparticle is expressly provided by the primary reference." See Office Action at page 7. The Office Action's remarks completely fail to engage applicants' argument that the reason for inclusion of PEG-DSPE in Papahadjopoulos's lipid microparticles would have been irrelevant if those compositions were to be entrapped in the polymer microparticles of Lunsford or Mathiowitz, as proposed by the Examiner.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 1-4, 6-16, 26, 29, 32-34, and 37.

At pages 8-10 of the final Office Action, claims 21-24, 26-28, and 31 were rejected as unpatentable over Lunsford in view of Papahadjopoulos. According to the Office Action, "it would have been *prima facie* obvious for one of ordinary skill in the art to include PEG-DSPE disclosed by Papahadjopoulos *et al.* in the microparticle of Lunsford et al., with a reasonable expectation of success, to produce the microparticle of the instantly claimed invention."

Lunsford describes microparticles containing a polymeric matrix, a nucleic acid, and a cationic lipid. Lunsford does not describe including in a microparticle a lipid (such as PEG-DSPE) having a pKa of less than about 2.5. Papahadjopoulos would not have provided the skilled person any reason to include PEG-DSPE in a microparticle of Lunsford.

As detailed above, Papahadjopoulos describes cationic lipid:nucleic acid complexes containing, among other components: (a) a cationic lipid; (b) a nucleic acid; and (c) a hydrophilic polymer. PEG-DSPE is described by Papahadjopoulos as an example of the "hydrophilic polymer" component of its complexes, not as an example of the "cationic lipid" component. The exemplary cationic lipids listed by Papahadjopoulos (at column 11, lines 6-7) include DODAC, DOTMA, DDAB, DOTAP, DC-Chol, and DMRIE. Nowhere does Papahadjopoulos suggest that PEG-DSPE can or should be used as the cationic lipid component in its complexes. Therefore, even if a person of ordinary skill in the art were to have selected a "cationic lipid" component

disclosed by Papahadjopoulos and use that cationic lipid as the cationic lipid in a microparticle composition of Lunsford, such a modification would not have resulted in the claimed compositions.

In addition to the foregoing, and as detailed above in response to the previous obviousness rejections, Papahadjopoulos describes the inclusion of the hydrophilic polymer PEG-DSPE in its cationic lipid:nucleic acid complexes as a means to prevent aggregation of the complexes and thereby enhance their shelf life. Because this anti-aggregation function of PEG-DSPE in the complexes of Papahadjopoulos would be irrelevant in the microparticles of Lunsford, the skilled person would have had no reason to make the modification proposed in the Office Action.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 21-24, 26-28, and 31.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 08191-0018001.

Respectfully submitted,

Date: August 17, 2009

/Jack Brennan/
Jack Brennan
Reg. No. 47,443

Fish & Richardson P.C.
601 Lexington Avenue
Floor 52
New York, NY 10022
Telephone: (212) 765-5070
Facsimile: (877) 769-7945